Challenges in diagnosing tuberculosis in settings with high HIV prevalence

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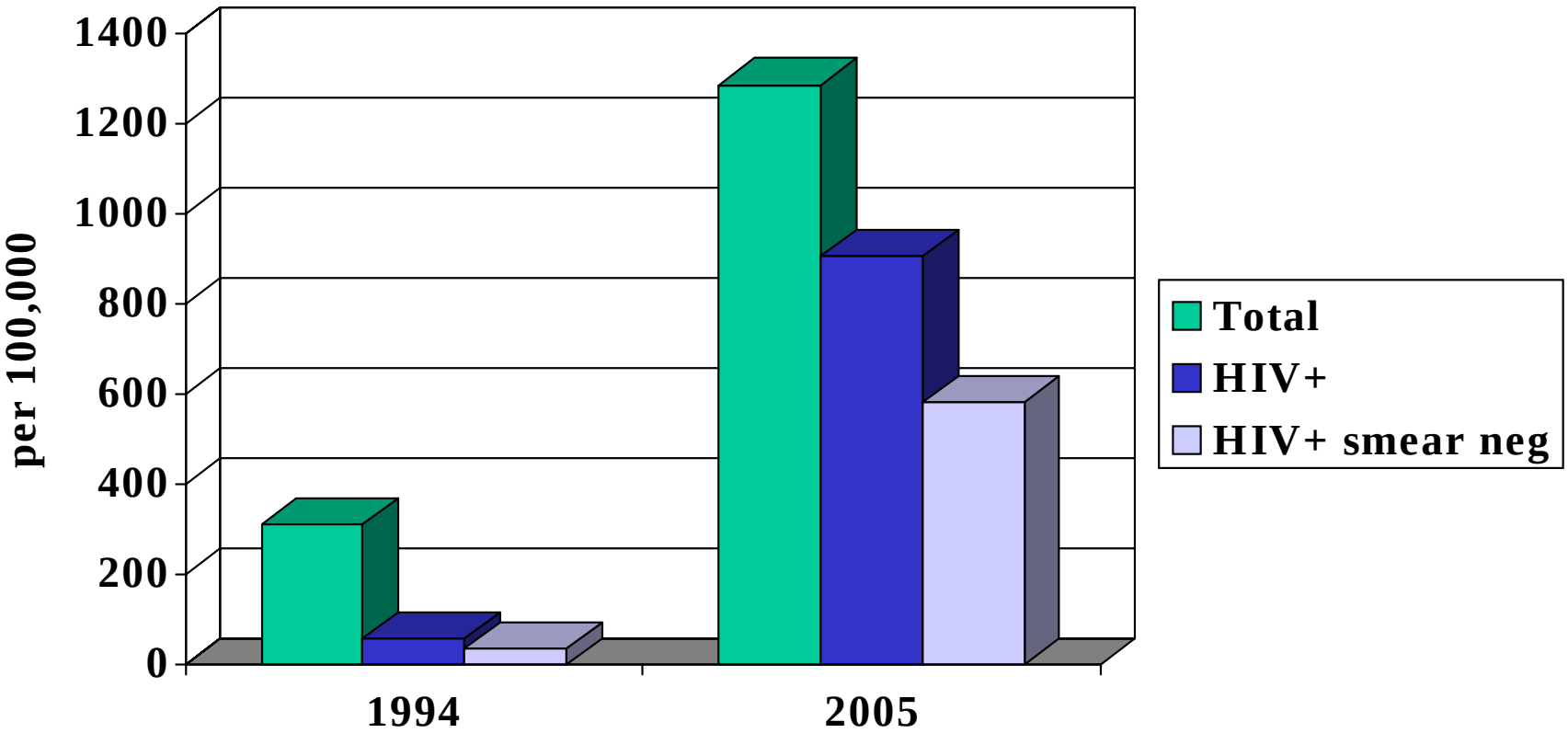
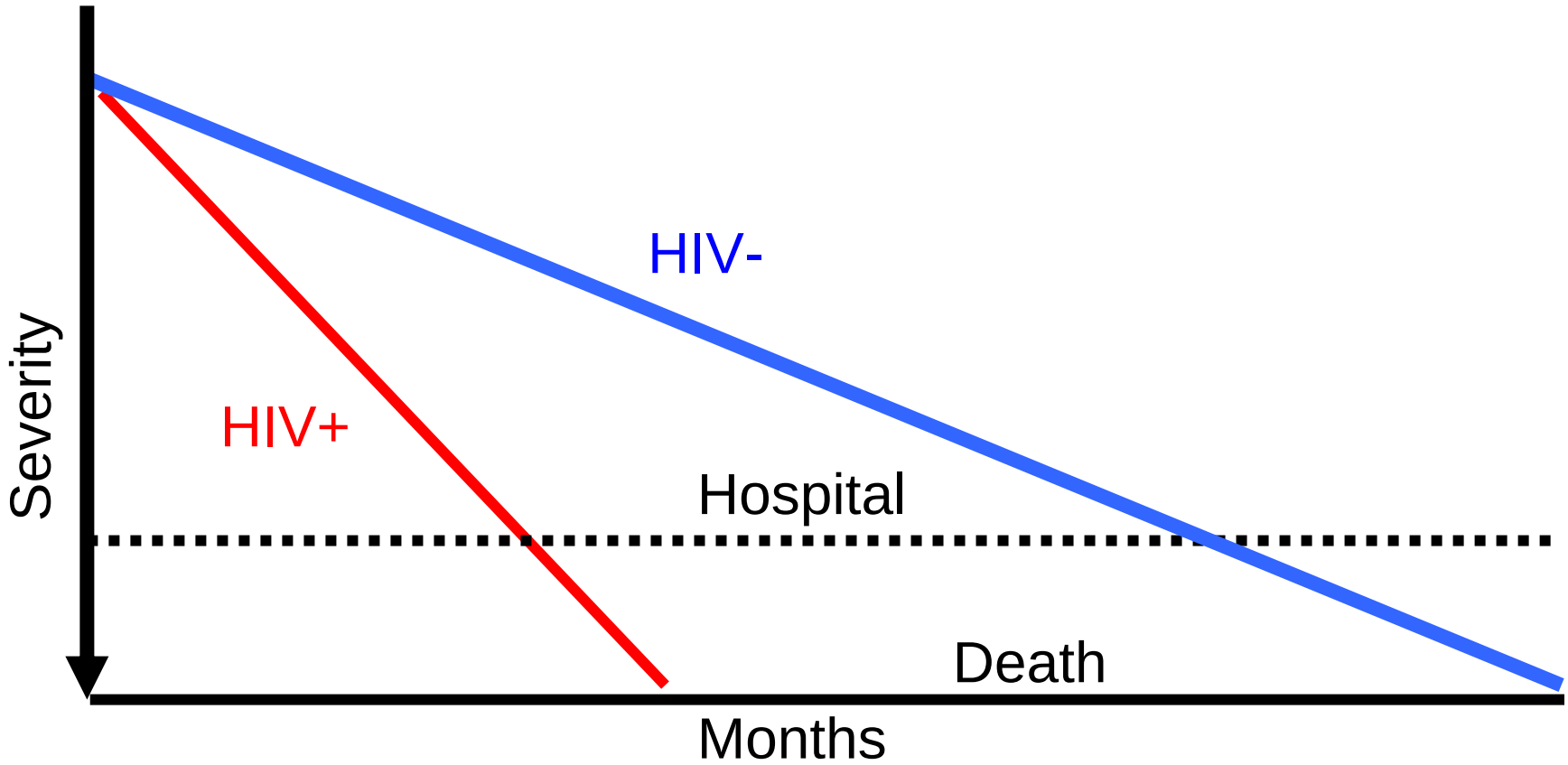
TB incidence in South Africa

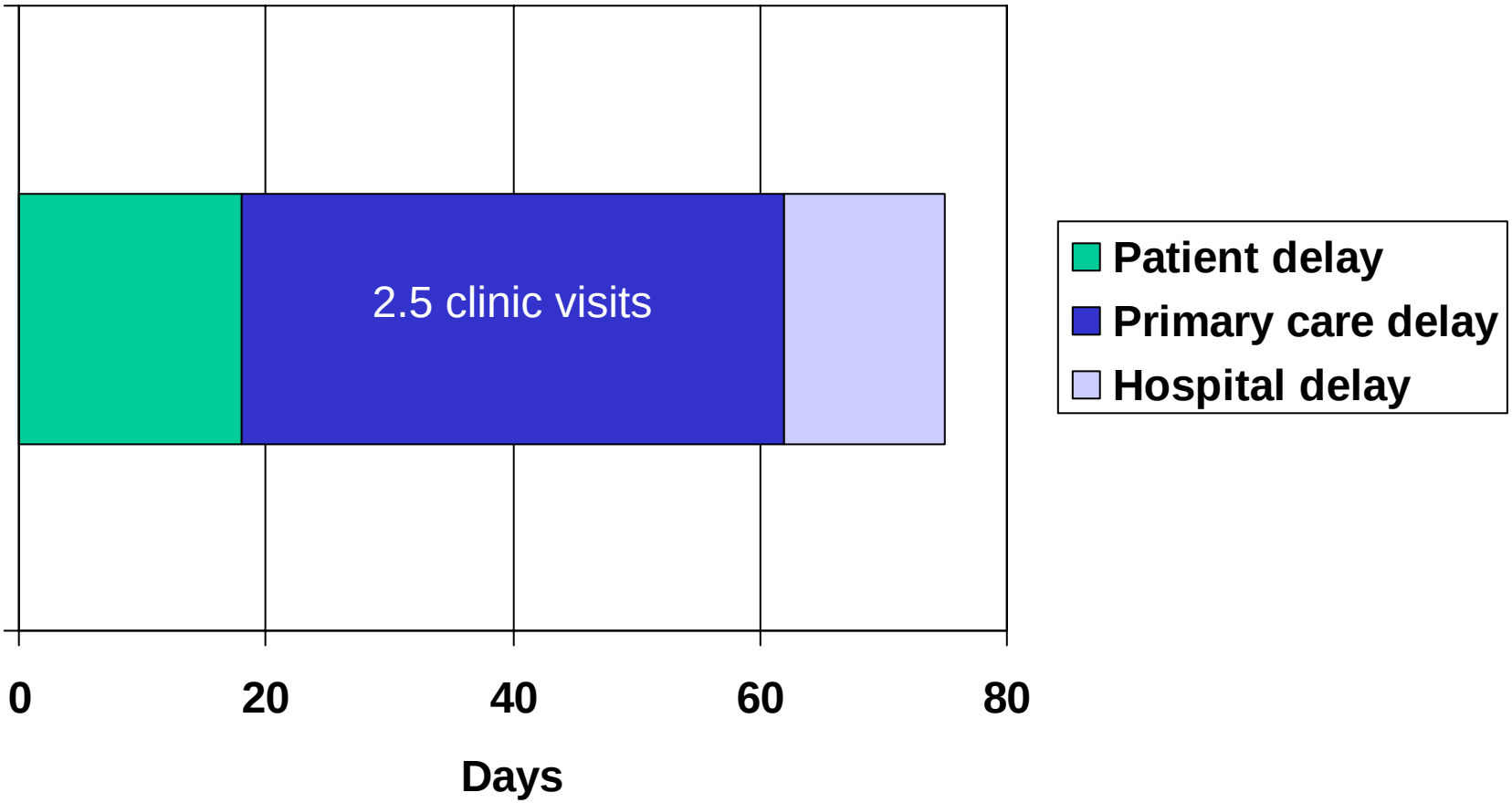


Fourie PB 2003

Course of TB



Diagnostic delay in ill TB suspects

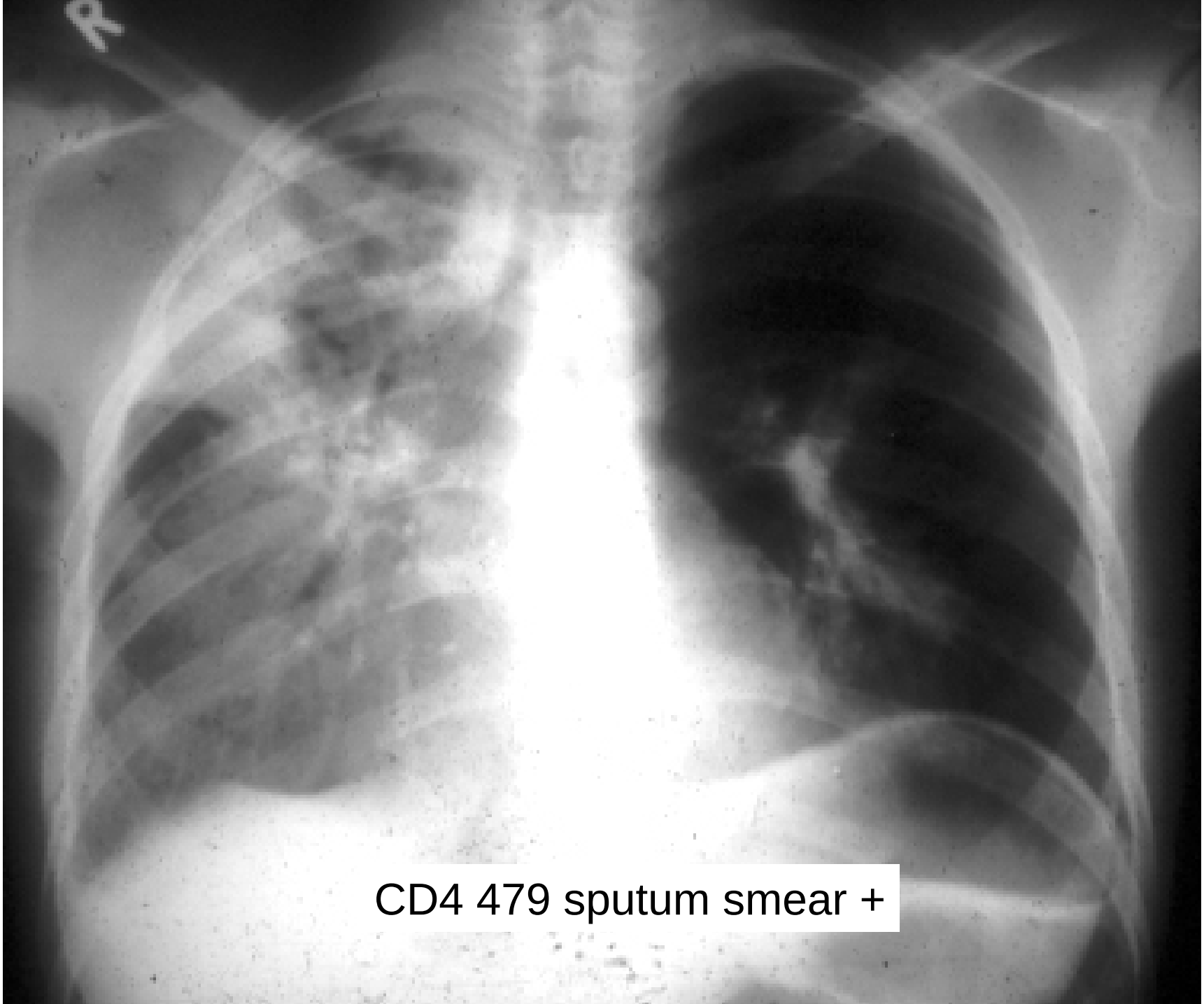


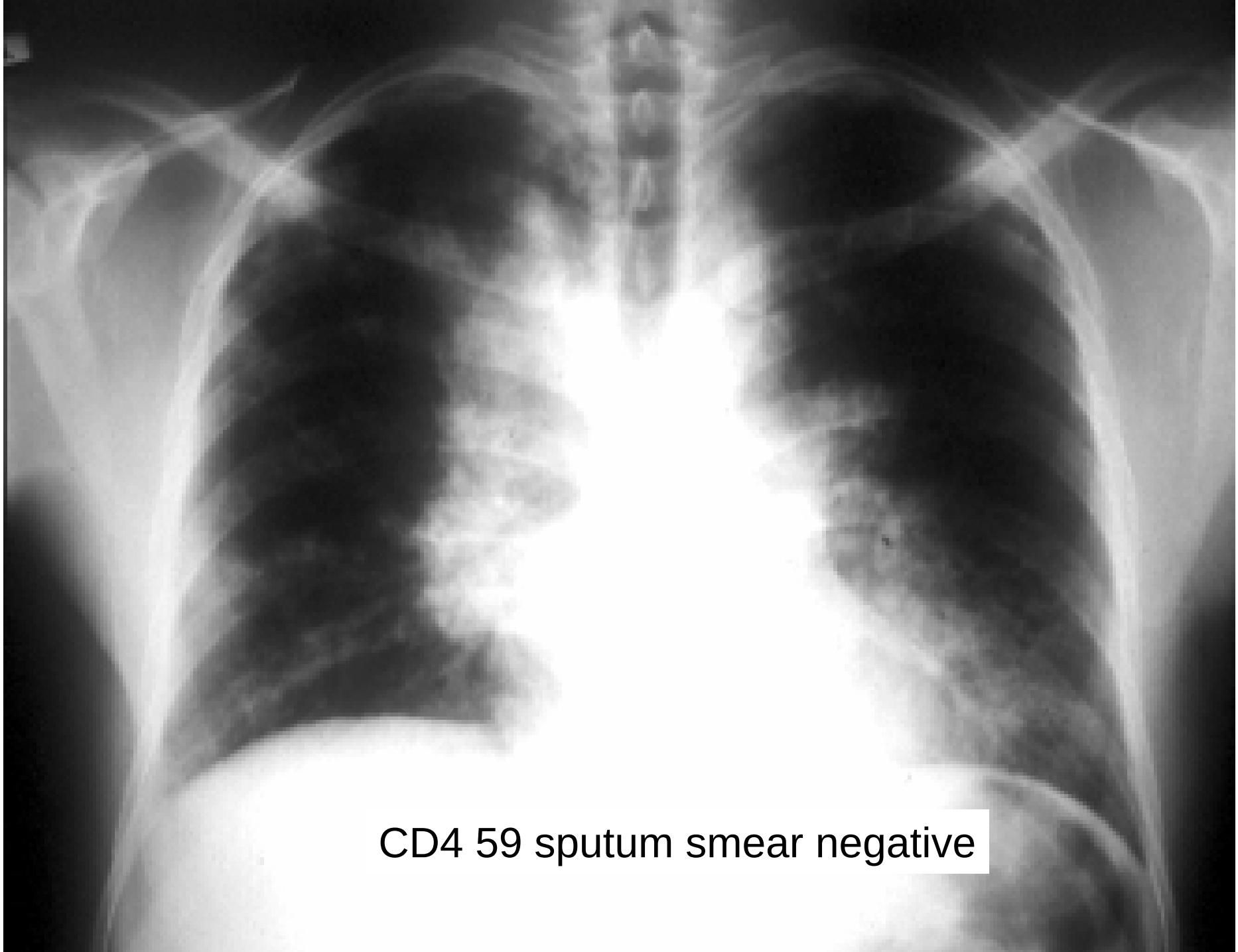
Meintjes G, et al. SA AIDS Conference, Durban 2003.
Hudson CP, et al. IJTLD 2000;4:240-5.

TB is the major cause of death in HIV-infected adults in Africa

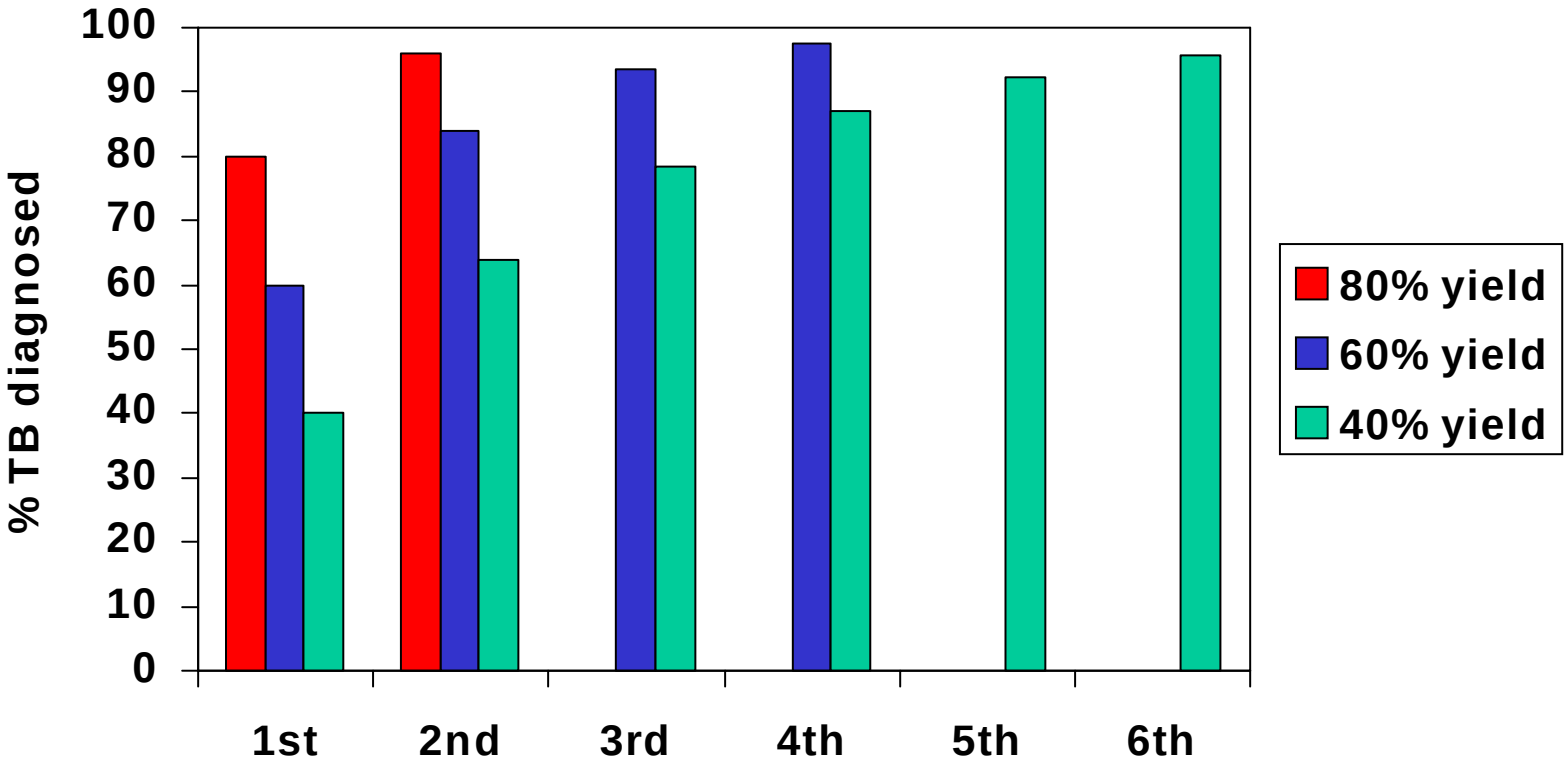
- Autopsy studies:
  - 32% Cote d'Ivoire
  - 38% Botswana
- Unrecognised

AIDS 1993;7:1569
Int J Tuberc Lung Dis 2002;6:55


CD4 479 sputum smear +


CD4 59 sputum smear negative

Sputum smear diagnosis

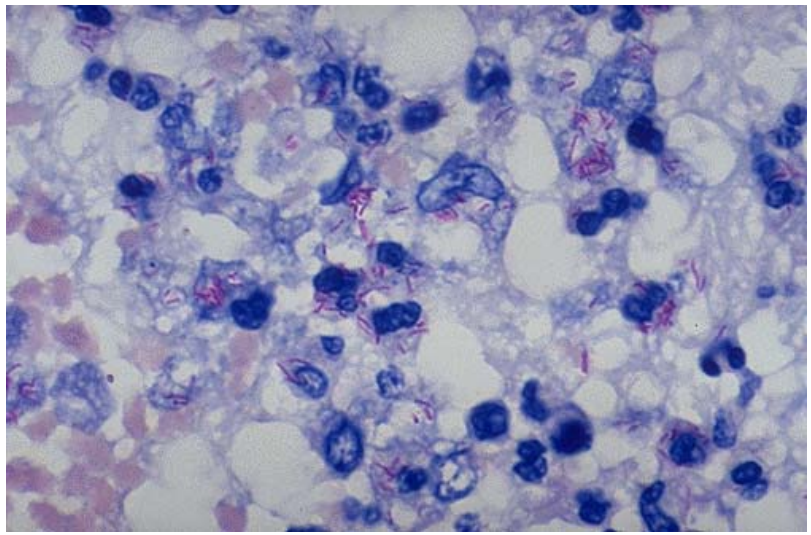


Sputum smear

Despite the limitations, sputum smear is still the BEST initial test and the only reliable RAPID test that we have.

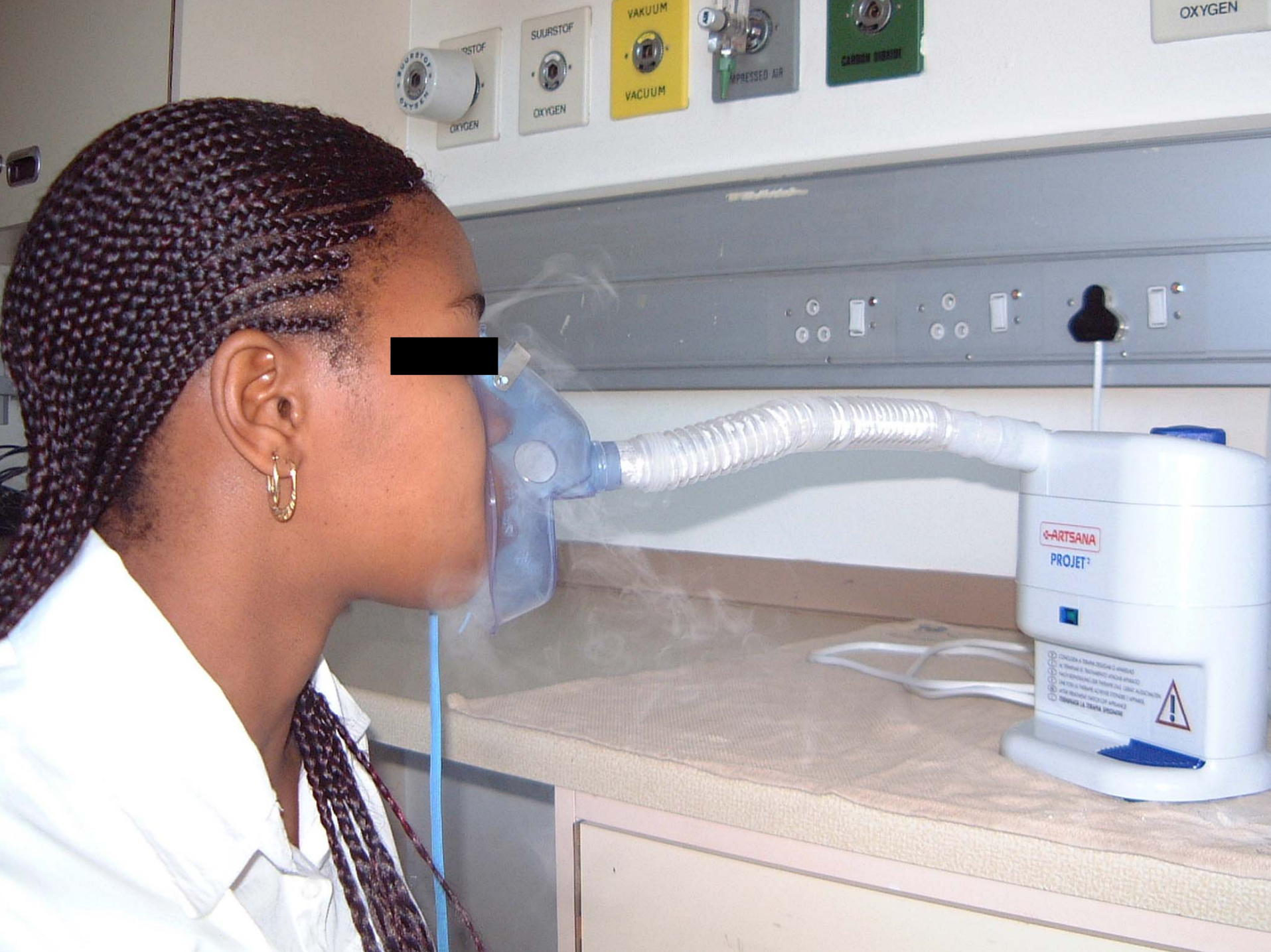
54/141 hospitalised HIV+ TB patients

Hudson C et al. IJTLD 2000;4:40



Induced sputum

- Malawi study
  - 41% culture positive
  - 25% smear positive (Tuber Lung Dis 1995;76:72-6)
- GF Jooste hospital, Cape Town
  - 72% culture positive
  - 27% smear positive (IJTLD 2006;10:31)
- Effective in children (Lancet 2005;365:130-4)
- Useful for confirming Pneumocystis pneumonia


SUURSTOF
OXYGEN
VAKUUM
VACUUM
OXYGEN
ARTSANA
PROJET

HIV-associated TB lymphadenitis

- 29% symmetrical, 30% are 2 cm or less
- Wide needle (19G) aspiration

  41% macroscopic caseation

  75% AFB positive
- Aspiration with intrathoracic TB

  71% AFB positive

(Bem 1995 & 1997, Pithie 1992)

Tru-cut biopsies nodes

High yield in children & adults

Jeena IJTLD 2000;4:139 & Wilson IJTLD 2005;9:220

New/investigational techniques

Phage assay

- Mycobacteriophage incubated directly
- Virucidal applied
- Plated onto rapid-growing mycobacterium
- Result 48 hours
- Sensitivity between smear & culture sputum
- Highly specific
- Most promising for diagnosing resistance
- Affordable
- Undergoing further development (FIND)

Visible results read by eye as plaques in a bacterial lawn(Left: negative result, Right: positive result)

Nucleic acid amplification tests (NAA)

- FDA licensed two kits for use in respiratory specimens, previously untreated patients with + smear (sensitivity smear neg ~50%)
- Extended to smear negative for RNA-based test if clinical suspicion of TB – based on clinical judgement (sensitivity smear neg 87%)
- Still need to do culture

TB Diagnostic Standards ATS/CDC Am J Respir Crit Care Med Vol 161. pp 1376–1395, 2000

Catanzaro et al. The role of clinical suspicion in evaluating a new diagnostic test for active tuberculosis. JAMA 2000;283:639

NAA extrapulmonary meta-analyses

- Commercial superior to in-house (bias)
- CSF (commercial NAA)
  - Sensitivity 56%
  - Specificity 98%
- Pleura (commercial NAA)
  - Sensitivity 62%
  - Specificity 98%

Pai M et al. 103rd ASM, 2003 & 37th California TB Controllers & ALA Spring Conference

Other diagnostic approaches

- Serodiagnosis hopeless
- Antigen detection - LAM promising
- Immune response (γ-IFN production)
  - Specific antigens for *M. tuberculosis* (ESAT-6 & CFP-10)
  - Diagnose latent TB infection
  - May be useful in serositis
- ADA - good ascites, pleura (with lymphocyte predominance), poor CSF

Clinical diagnosis

Excluding TB before preventive therapy in patients with clinically advanced HIV

- Any two of:
  - Weight loss > 2.5%
  - Cough > 2 weeks
  - Fever > 2 weeks
  - Night sweats > 2 weeks
- sensitivity 100% specificity 88%

Mohammed A et al. IJTLD 2004;8:792-5.

Value of chest radiography in a tuberculosis prevention programme for HIV-infected people, Botswana

B Mosimaneotsile, E A Talbot, T L Moeti, N M Hone, G Moalosi, H J Moffat, E J Lee, T A Kenyon

1 of 563 (0.2%) with no signs/symptoms TB was

diagnosed with tuberculosis on the basis of the CXR

Lancet 2003; **362:** 1551–52

WHO case definition for smear negative pulmonary TB

- Pulmonary
  - 3 negative smears sputa
  - No response antibiotics
  - Compatible radiograph
- Malawi 78% TB (only ½ confirmed)
- Need to incorporate PCP if HIV+

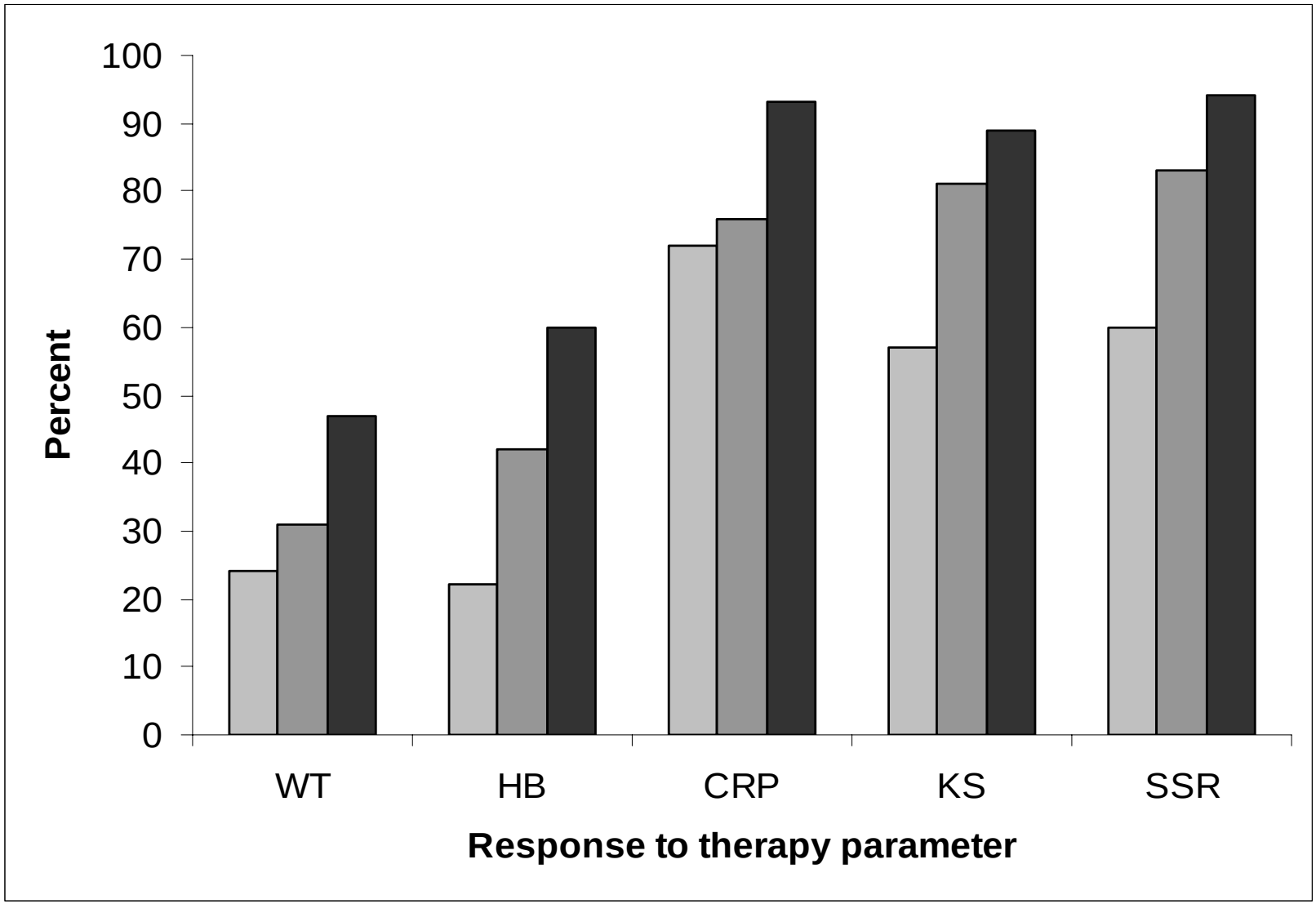
Hargreaves 2001

UCT SNTB study, regional hospital

Case definition	Number	TB diagnosis		Sensitivity
		Confirmed	Response to therapy	
Pulmonary	83	64	10	89%
Lymphadenitis	118	102	9	94%
Serositis	36	25	9	94%
Constitutional	11	4	0	36%

Wilson D et al. IJTLD 2006;10:31

Response to empiric TB therapy in smear negative TB



Case definitions in primary care

- Mostly pulmonary
- Effective in Khayelitsha (Saranchuk Durban 2005)
- Evaluation in East Street Clinic, Pietermaritzburg

Conclusions

- Recent rapid increase in burden of smear negative TB due to HIV
- Smear still the only rapid test
- Better specimens (induced sputum, lymph node aspirate) increase yield
- Some NAA tests promising, but still lack sensitivity if smears negative – need clinical input
- Symptoms/signs can rule out TB before IPT or HAART
- Clinical case definitions useful & currently only feasible approach in resource-limited settings